ABSTRACT

Established agents such as lithium, divalproex sodium, and carbamazepine have been in use for several decades for the treatment of bipolar disorder. Over the past few years, several new agents have become available, notably second-generation antipsychotic drugs. Although the ultimate goal of treatment in bipolar disease is to establish and sustain full remission, this is not always feasible. Providing symptomatic relief while minimizing adverse effects, preventing suicide, and ensuring an acceptable quality of life are appropriate and meaningful goals. The availability of a larger number of drugs that can be used for treatment of bipolar disorder should facilitate the achievement of these goals.

In recent years, options available for the pharmacotherapy of bipolar disorder have increased significantly. Despite this fact, treatment of this devastating mental disorder remains far from satisfactory. Indeed, many patients, even when in remission from the acute episode, continue to experience between episodes subthreshold symptoms that contribute to social, occupational, and cognitive dysfunction.

Numerous reasons account for the unsatisfactory rate of treatment success; one is the complexity of the disease, with its phases of mania, depression, mixed mood, and rapid cycling, each necessitating different treatment strategies. Evaluation of treatment outcomes in clinical practice is also not straightforward. Indeed, no clear definition has been decided upon for a treatment response in bipolar disorder. Although reduction in the symptoms of mania may rightly be considered a treatment response, longitudinal stability is more relevant because effective short-term treatment of mania may give way to depression, and vice versa. Attempts to fully manage a particular set of bipolar disorder symptoms may increase the risk that symptoms of the other pole will be induced. Additionally, escalating doses of an agent can lead to severe medication-related adverse effects that are not well tolerated over the course of the illness (particularly when symptomatic stability has been achieved). Indeed, medication compliance is poor in patients with bipolar disorder. With the increasing availability of new drugs for the treatment of bipolar disorder, the choice of agent has become a complex one. This article reviews the range of drugs currently used in the treatment of bipolar disorder.

CHOICE OF MEDICATION

A wide range of drugs may be used for treatment of the many phases of bipolar disorder. These drugs can be broadly divided into 2 main categories—mood stabilizers and antipsychotics (typical and atypical). However, as discussed here, in the absence of agreed-upon definitions, the delineation of these categories is ambiguous.

MOOD STABILIZERS

The term mood stabilizer is firmly entrenched in the lexicon of bipolar disorder treatment, yet it is not recognized by the US Food and Drug Administration...
Lithium has been the mainstay of bipolar disorder treatment since the 1960s; numerous studies, including placebo-controlled trials, have provided data demonstrating its efficacy in treating manic and depressive episodes and in maintenance therapy. The effect of lithium on control of manic symptoms and prevention of relapse appears to be greater than its antidepressant effect, although the drug does possess antidepressant efficacy. Lithium therapy may also reduce suicidal risk in bipolar patients—a finding of great public health significance. However, lithium has several limitations, including inadequate response in some patients (especially those with mixed moods or rapid cycling), a narrow therapeutic range, and an unfavorable adverse effect profile (eg, gastrointestinal dysfunction, tremor, thirst, polyuria, weight gain, hypothyroidism, renal toxicity).

Anticonvulsants, particularly divalproex sodium and carbamazepine, are now widely used for the treatment of acute episodes of mania and for prophylaxis. The use of divalproex sodium has increased significantly over the past few years, and it is now prescribed more frequently than lithium. Evidence reveals superior efficacy of divalproex sodium over lithium for the treatment of acute mania. Furthermore, divalproex sodium may be more effective at higher doses. Limitations of divalproex sodium include the need for regular blood testing and its unfavorable adverse effect profile (eg, gastrointestinal dysfunction, tremor, thirst, polyuria, weight gain, hypothyroidism, renal toxicity).

Other anticonvulsants under investigation for bipolar disorder include gabapentin, tiagabine, topiramate, oxcarbazepine, and zonisamide. Results to date have been mixed, perhaps suggesting that anticonvulsants do not have a class effect in bipolar disorder. These agents have often been studied in small clinical trials and in open-label case series. We therefore must await the results of ongoing large-scale studies before we will be able to fully appreciate their role (or lack thereof) as mood stabilizers.

**Antipsychotics**

First-generation antipsychotics. Conventional, typical, or first-generation antipsychotics (FGAs) have a rapid and powerful effect on symptoms of mania, especially psychomotor agitation. However, long-term treatment with FGAs is associated with an increased incidence of tardive dyskinesia and prolactin elevation; moreover, evidence suggests that this adverse effect tends to be more severe in patients with bipolar disorder than in patients with schizophrenia. Furthermore, FGAs may precipitate depression in patients with bipolar disorder.

Second-generation antipsychotics. Atypical antipsychotics, or SGAs, have now been established as first-line therapy for schizophrenia and other psychoses. Recently, they have also emerged as effective agents for the treatment of bipolar disorder.

Clozapine, the prototype of SGAs, has shown efficacy in the treatment of bipolar disorder; however, mirroring its use in schizophrenia, where it is restricted to second-line treatment (because agranulocytosis develops in some patients), it has been studied mainly for use in the treatment of refractory bipolar disorder.

Olanzapine was the first SGA to be granted FDA approval (in 2000) for the treatment of acute mania. It has been studied extensively in mood disorders. Its
efficacy in the treatment of acute mania was demonstrated in 2 double-blind, placebo-controlled trials and in a comparative trial with lithium, which showed it to be at least as effective as lithium. Its efficacy has also been compared with that of divalproex sodium. In a single trial, olanzapine was shown to be more effective than divalproex sodium; in another, both agents had equal efficacy, but divalproex was associated with a more favorable adverse event profile.

The remaining SGAs—risperidone, quetiapine, ziprasidone, and aripiprazole—have all demonstrated efficacy as monotherapy in the treatment of acute mania. In addition to olanzapine, quetiapine, ziprasidone, and aripiprazole have received FDA approval for the treatment of acute mania. The results of the FDA registration studies are all broadly similar and confirm an acute antimanic effect for SGAs. Obviously, direct comparisons between agents cannot be made from these studies; however, in general terms, evidence suggests similar short-term efficacy across all SGAs in the treatment of acute mania.

Evidence for the efficacy of SGAs in the maintenance treatment of bipolar disorder is more limited. Olanzapine has received approval for maintenance therapy and for the treatment of bipolar depression in combination with fluoxetine. In a placebo-controlled trial, olanzapine was shown to delay relapse in bipolar disorder. Preliminary data from open-label trials indicate that quetiapine monotherapy and risperidone combined with a mood stabilizer are effective in the maintenance treatment of bipolar disorder. Aripiprazole has also shown promise, and in 2 long-term studies (12 and 26 weeks), the time to relapse of symptoms was significantly longer with aripiprazole than with haloperidol or placebo. Some evidence indicates that the combination of an atypical antipsychotic with a mood stabilizer may be superior to use of a mood stabilizer alone. Combinations with carbamazepine should be considered carefully because this agent is associated with significant drug-drug interactions.

At the present time, it is less clear whether combination therapy (and which type) is better than monotherapy in the maintenance treatment of bipolar disorder. Clinicians appear to favor combination therapy, but the rationale for one particular combination over another has yet to be established. Additionally, although clinicians can attempt to select drug combinations that are less likely to aggravate (or synergize with) the adverse effects of individual agents, in practice, this is a complex task because of overlap between agents in their adverse effect profile. The propensity of many mood-stabilizing agents and antipsychotics to cause sedation and weight gain exemplifies this overlap.

It must be acknowledged, therefore, that the expectation of efficacy of SGAs, as monotherapy or in combination with mood stabilizers, is accompanied by risk and concern about adverse effects. Although some agents (ziprasidone, aripiprazole) appear to have a more favorable adverse effect profile than others (olanzapine, clozapine), and others (risperidone, quetiapine) continue to have an intermediate profile, it is important to note that (based on current evidence) all these drugs are associated with the potentially serious adverse effects of weight gain, diabetes mellitus, dyslipidemia, and other metabolic disturbances. In view of the long-term risks and complications associated with these effects, clinicians must be vigilant in monitoring weight and metabolic indices over time. The impact of emerging guidelines on the use of SGAs in the maintenance treatment of bipolar disorder is presently unclear. Nevertheless, these significant adverse effects are likely to affect clinicians’ decisions regarding acute and maintenance treatment of bipolar disorder.

CONCLUSION

Long-term treatment of bipolar disorder remains a challenge. Nevertheless, the greater availability of agents that can be used as monotherapy or as part of combination therapy offers hope for better treatment outcomes. Choice is an important issue in consumerism, and even though the complexity of treatment and the risk-benefit analysis are better understood now, the availability of more agents means that patients have greater choice. Wise choices of clinicians that are made with full involvement of patients are an important goal of treatment. Treatment of bipolar disorder is a rapidly evolving area of psychopharmacology. Clinicians and patients alike must stay informed about ongoing developments and study results (particularly head-to-head comparator studies).

The challenge that clinicians face today involves how to match an appropriate agent with each patient. This choice should be based on all available efficacy and tolerability information and should be made in consideration of the patient’s medical history, thereby maximizing the potential for improvement while minimizing the risk of adverse effects and avoiding the exacerbation of existing risk factors.
REFERENCES


